Myocardial Viability by DE-MRI and Low-dose Dobutamine CMR

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Introduction

Dysfunctional myocardium that remains viable has the potential for contractile recovery after reperfusion.[1] Dysfunctional but viable myocardium has been broadly divided into two closely linked pathophysiological states, myocardial hibernation and stunning. Stunned myocardium is the result of an ischemic insult leading to contractile dysfunction despite adequate reperfusion. Hibernating myocardium describes down-regulation of myocyte metabolism as a result of prolonged reduction in perfusion, or, in some cases, from repetitive episodes of myocardial stunning.[2] Until recently scintigraphic techniques and stress echocardiography were the mainstay of diagnosis.[3;4] The focus of this presentation is on the rapidly emerging clinical role of cardiovascular magnetic resonance imaging (CMR) in the detection of viable myocardium.

Delayed Enhancement MRI

CMR has the unique ability to evaluate several markers of myocardial viability that are of proven value. Reliable and accurate assessment of myocardial scar burden[3], coronary perfusion[4], and contractile reserve[5] by CMR are all becoming well established.

Direct imaging of myocardial fibrosis is now possible using an inversion-recovery prepared T1-weighted gradient-echo sequence following the intravenous administration of a gadolinium-chelate (Gd). This CMR technique has been named "delayed-enhancement" (DE-MRI) and demonstrates non-viable tissue as "hyperenhanced" or bright. Both interstitial and replacement fibrosis hyperenhance similarly with DE-MRI for reasons described below. The hyperenhancement of interstitial fibrosis is more commonly seen (and recently described) in infiltrative entities such as hypertrophic cardiomyopathy, where the issue of viability is less prominent.[6,7]

The majority of recent published data supports the notion that the hyperenhanced regions have sustained irreversible ischemic injury.[8-14] While many investigators have evaluated the use of contrast enhancement in myocardial infarction throughout the 1980's and 1990's, Kim, et al., published the initial manuscript describing what is now known as the DE-MRI technique.[8] In this seminal study in a canine model, the left anterior descending artery was instrumented and occluded either transiently or permanently. DE-MRI of the explanted hearts were compared to TTC stained pathology specimens at 1 day, 3 days, or 8 weeks post instrumentation, with near perfect correlation demonstrated between hyperenhancement on MRI and irreversible damage at pathology.[8]

These findings laid the foundation for subsequent investigations in humans demonstrating that the extent of hyperenhancement on a segmental or regional basis is a critical determinant of contractile recovery.[10] Forty-one patients with chronic ischemic disease undergoing revascularization demonstrated that on followup studies 2½ months following revascularization,

dysfunctional segments with <25% hyperenhancement had an increased likelihood of functional recovery, while dysfunctional segments with >50% hyperenhancement had little chance of functional improvement.[10] This spectrum in potential for contractile recovery is consistent with observations from stress echocardiographic studies, demonstrating that the hibernating myocardium has a continuum of histological and biochemical perturbations that define its ability to recover.[15,16]

Rehwald, et al., recently provided further convincing evidence that DE-MRI is highly specific for irreversibly injured myocardium.[17] These authors used electron probe x-ray microanalysis (EPXMA) to simultaneously examine concentrations of Gd, Na, P, S, Cl, K, and Ca in myocardium, and histological staining to define areas of scar. Acute and chronic infarction, and at risk peri-infarction zones were analysed. Compared with remote regions, Gd levels measured by EPXMA were more than doubled in acutely infarcted non-viable areas and were four-fold higher in chronically infarcted regions. The concentration of Gd was not elevated after reperfusion in regions that were considered at risk, but not infarcted. This work confirms that elevations in myocardial Gd are confined to regions of histologically defined irreversible ischemic injury.

Preliminary observations suggest that the high spatial resolution of contrast-CMR may also allow further refinement of risk-stratification in patients with acute myocardial infarction containing areas of microvascular obstruction. Wu, et al., in a series of 44 patients 10±6 days after infarction, found that microvascular obstruction (defined as hypoenhancement seen 1 to 2 minutes after contrast injection), was a significant marker of post-infarction complications.[18] Similar findings have been shown on contrast echocardiographic studies.[19] Recently, the direct visualization of discrete microinfarctions following percutaneous coronary interventions also has provided further insight into peri-procedural elevations in creatine kinase-MB enzyme levels.[20]

As discussed above the excellent spatial resolution and tissue characterization afforded by CMR makes it ideal for both: 1) quantification of significant areas of viable myocardium, and 2) defining discrete regions of non-viability. Accurate quantification of areas of scar and viable tissue is clearly important in predicting mortality as the benefits of revascularization rise steeply when the area of dysfunctional but viable myocardium reaches a critical size.[21-23]

As technology continues to progress, the clinical utility of contrast-enhanced MRI in the detailed analysis of myocardium and scar tissue will have a wider clinical role.

Contractile Reserve (Dobutamine Stress Cardiac MRI (DSMRI))

The value of assessing inotropic reserve in the detection of viable myocardium by DSE is well established, and has been reviewed extensively.[24] DSMRI in detecting coronary ischemia and viability using the same underlying principles has rapidly emerged as a comparable technique. Recent studies have confirmed that both low-dose and high-dose DSMRI are at least equivalent if not of superior accuracy compared to DSE.[5,25-29]

Baer FM, et al., performed low-dose dobutamine transesophageal echocardiography (Dob-TEE) and low-dose DSMRI studies in 103 patients after myocardial infarction.[30] The positive and negative predictive accuracies of Dob-TEE and DSMRI for the prediction of left ventricular functional recovery after revascularization were similar (85% vs 92%, ns, and 80% vs 85%, ns). Baer, et al., in a separate study, evaluated viability by MRI following myocardial infarction comparing to [18F]fluorodeoxyglucose–positron emission tomography (PET) as the gold standard.[31] Patients with myocardial infarction (infarct age > 4 months) were studied with low-dose DSMRI examinations, with viability defined by an end-diastolic wall thickness of 5.5

mm or more and evidence of dobutamine-induced systolic wall thickening of greater than 1 mm. When both these parameters were used as criteria for viability, DSMRI demonstrated a sensitivity of 88% and specificity of 87%. With regard to end-diastolic wall thickness as a marker of viability the findings of Baer, et al., closely resemble that of Cwajg, et al., who compared DSE to rest-redistribution thallium-201 (T1-201).[32] The latter investigators showed that a combination of end-diastolic wall thickness by echocardiography and inotropic reserve had a sensitivity of 88% for detecting viability They also demonstrated a similar threshold for end-diastolic wall thickness ($\leq$ 6 mm) below which functional recovery was unlikely.

In general DSMRI allows better endocardial definition and substantially reduces the incidence of poor quality studies. The potential importance of this has been clearly demonstrated by Hundley and colleagues who studied a series of patients referred for DSMRI as a result of inadequate acoustic windows for stress echocardiography.[33] In this series, inducible ischemia on DSMRI conferred an annual event rate of 10.6% for cardiac death or myocardial infarction, a rate similar to patients with ischemia detected by stress echocardiography (1-year event rates of 7% to 11%). Demonstrable inotropic reserve in resting akinetic segments (consistent with myocardial viability) was also significantly associated with myocardial infarction and cardiac death, and is concordant with observations made using DSE.[21] In Hundley's series no patients without ischemia and an ejection fraction >60% had cardiovascular events during the 2 year follow-up period, findings comparable to the event rate found in exercise echocardiogram and Tl-201 scintigraphy (0.5% to 0.85% per year).[34]

CMR Compared to other Techniques

Currently, there is limited prognostic data in patients with myocardial viability as assessed by cardiac MRI. However, there is a wealth of literature on the use of scintigraphic techniques (PET, SPECT) and DSE for identifying high-risk patients in whom survival could be prolonged by revascularization. In general, SPECT perfusion studies and DE-MRI have greater sensitivity but lower specificity for identifying viable myocardium compared to techniques that detect contractile reserve (i.e., Dob-MRI and DSE).[35,36] Data on prognosis based on Dob-MRI assessment of viability has only just begun to emerge.[37] Nonetheless, results of contractile response with dobutamine protocols are essentially identical in the majority of studies for both Dob-MRI and DSE. It is therefore reasonable to project that much of the extensive prognostic data available for DSE could be extrapolated to Dob-MRI.

DE-MRI has shown excellent accuracy in the delineation of scar when compared with scintigraphic techniques. Klein, et al., studied 31 patients with ischemic cardiomyopathy and found a close correlation between the extent of myocardial scar identified by DE-MRI and PET.[38] Though quantitative assessment of infarct mass by DE-MRI correlated well with PET infarct size (r=0.81, P<0.0001), DE-MRI identified subendocardial scar more frequently than PET. These authors also compared wall thickness (end-diastolic and end-systolic) and wall thickening at rest in combination with DE-MRI for viability, using PET as the gold standard, and found significantly better results for DE-MRI based on ROC analysis. These findings are concordant with those of Wagner, et al. who recently compared DE-MRI with SPECT in 91 patients.[39]

The clinical reproducibility of infarct size by DE-MRI has been evaluated and compared with the reproducibility of SPECT imaging by Marholdt, et al. In this study the size of chronic infarcts (which were between 4% and 27% of total LV mass as measured by DE-MRI) showed

no significant change in size between 10 and 30 minutes after contrast administration, and compared favourably with quantitation by SPECT.[3]

Conclusion

Cardiovascular MRI provides a unique tool to assess multiple interrelated clinical markers of viability in a single test. Its overall accuracy appears to be equivalent, and in several reports superior to the currently available techniques, including PET imaging. Considering the greater spatial resolution compared to PET and the wealth of correlative pathological data, DE-MRI may well represent the new gold standard in the detection of irreversibly damaged myocardium.

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